Acute Coronary Syndromes

Characteristics, management and prognosis in relation to gender and type of syndrome

Elisabeth Perers

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To my family

CONTENTS

ABSTRACT

Background: Acute coronary syndromes (ACS) represent a wide spectrum of conditions from ST-elevation myocardial infarction (STEMI) to unstable angina pectoris (UAP). Randomized trials tend to focus on ST-elevation myocardial infarction (STEMI) or non-ST-elevation ACS, and consequently studies providing data on the entire condition are relatively scarce, especially with information including long-term follow-up.

Methods: We studied 1744 consecutive patients under 80 years of age admitted to the coronary care unit (CCU) at Sahlgrenska University Hospital with ACS between Sept 1995 and Sept 1999. The patients were divided into four groups with assumed decreasing order of severity on the basis of ECG and biochemical markers; STEMI, non STEMI and UAP of high-and low-risk types. Three different age groups were also created (<65, 65-74 and 75-79 years). All patients were followed for 5 years with regard to total mortality and for 45 months with respect to cardiovascular morbidity and mortality. The main objectives were to study differences in baseline characteristics, clinical presentation, treatment, early as well as long-term morbidity and mortality in relation to gender, type of syndrome and age.

Results: Women were older than men, less likely to seek early medical care, and in the younger age group more likely to present with hypotension. No significant differences in treatment were observed. Reperfusion was used to a similar extent in women and men, but there was a non significant tendency to use percutaneous coronary intervention (PCI) more often in men. Women did not suffer from more severe complications or early deaths. Among women and men surviving the acute phase there was no difference in long-term mortality (21.0% and 18.2%, respectively). After adjustment for age differences the hazard ratio (HR) and corresponding confidence interval (CI) for a higher late 5 year mortality in women in relation to men was 0.89 (0.70-1.13), p=0.34. The crude rate of rehospitalization for congestive heart failure was significantly higher in women, a significance that disappeared after adjustment for age. While short-term mortality was highest in STEMI, the non STEMI patients did worse in the long run. Non STEMI was associated with a significantly higher long-term mortality than STEMI, before but not after adjustment for co-variates (HR and 95% CI 1.02 [0.75-1.37], p=0.92). Of these, age, ST-depression on admission and early revascularization with PCI seemed to be of particular importance.

Elderly patients had a more complicated course of the disease, were less frequently subjected to coronary angiographies and PCI, and had a poorer outcome. Patients with UAP, especially of the low-risk type, experienced poorer quality of life following ACS than patients with other types of ACS.

Conclusion: Among patients <80 years with ACS admitted to a CCU, the suspicion that women are treated less aggressively and suffer from more complications including mortality than men could not be verified. Only small gender differences were observed. With respect to type of syndrome we could demonstrate a higher long-term mortality in non STEMI, which disappeared after adjustment for variables with a significant impact on prognosis.

Key words: Acute coronary syndromes, gender, age, treatment, quality of life, outcome

LIST OF ORIGINAL PAPERS

This thesis is based on the following papers which will be referred to in the text by their Roman numerals:

I

E. Perers, K. Caidahl, J. Herlitz, M. Sjölin, B. W. Karlson, T. Karlsson, M. Hartford
Spectrum of acute coronary syndromes: History and clinical presentation in relation to sex and age
Cardiology 2004:102:67-76

II

E. Perers, K. Caidahl, J. Herlitz, B. W. Karlsson, T. Karlsson, M. Hartford
Treatment and short term outcome in women and men with acute coronary syndromes
Int J Cardiology 2005;103:120-127

III

E. Perers, M. From Attebring, K. Caidahl, J. Herlitz, T. Karlsson, P. Währborg, M. Hartford
Low risk is associated with poorer quality of life than high risk following acute coronary syndrome
Coronary Artery Disease 2006;17:501–510

IV

E. Perers, K. Caidahl, J. Herlitz, T. Karlsson, M. Hartford
Impact of diagnosis and gender on long-term prognosis in acute coronary syndromes.
Submitted for publication in American Heart Journal

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
BPM	Beats Per Minute
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CHP	Cardiac Health Profile
CI	Confidence Interval
CK	Creatine Kinase
ECG	Electrocardiogram
ED	Emergency Department
HR	Hazard Ratio
LBBB	Left bundle Branch Block
LMW	LowMolecularWeight
MI	Myocardial Infarction
NSTEMI	Non ST Elevation MI
PCI	Percutaneous Coronary Intervention
PEA	Pulseless Electrical Activity
QoL	Quality of Life
RBBB	Right Bundle Branch Block
STEMI	ST Elevation MI
UAP	Unstable Angina Pectoris
UAPHR	UAP High Risk
UAPLR	UAP Low Risk
VF	Ventricular Fibrillation
VSD	Ventricular Septal Defect
VT	Ventricular Tachycardia

INTRODUCTION

Acute coronary syndrome (ACS) is a major cause of morbidity and mortality in Sweden and worldwide. ACS comprises a broad spectrum of clinical conditions from unstable angina pectoris (UAP) with no ischemic ECG changes or biochemical evidence of myocardial necrosis to ST-segment elevation myocardial infarction (STEMI) and sudden coronary death. Manifestations of coronary artery disease (CAD) in populations undergo rapid changes over time. In many countries the incidence of myocardial infarction (MI) and the mortality from CAD is decreasing [1,2] Furthermore, the severity of ACS has changed due to effective preventive measures together with improvements in management and treatment[3]. In spite of these positive trends ACS continues to be associated with considerable morbidity and mortality.

Pathophysiology

Coronary atherosclerosis starts early in life. Coronary lesions are present in the majority of young adults, particularly in western countries. Proliferation of smooth muscle cells, matrix synthesis, and lipid accumulation may narrow the arterial lumen gradually and lead to myocardial ischemia and anginal pain, but survival is good if thrombotic complications can be prevented[4,5]. Atherosclerosis is primary located in the intimae of the vessel wall. A healthy endothelium functions as a selective lipoprotein–permeable barrier.

Dysfunction of the endothelium can be caused by stress, turbulent blood flow and factors such as diabetes, smoking, hyperlipidemia, hypertension and /or genetic mechanisms[6]. During the last decades inflammatory reactions are recognized to be involved in the process of atherosclerosis. In the presence of endothelium dysfunction, inflammatory cells and lipid laden foam cells will migrate into the arterial vessel wall[7]. Atherosclerotic plaque formation is a slow and insidious process, which can continue for many years before overt symptoms. The mechanism responsible for the sudden conversion from a stable disease into a life–threatening condition is either endothelial erosion or plaque disruption, the former more common in women and the latter in men, both triggering thrombosis formation[8,9]. The risk of plaque disruption depends more on plaque vulnerability and thrombogenecity than on plaque size or severity of stenosis[10,11].

Coronary plaques are constantly stressed by a variety of biochemical, mechanical and hemodynamic forces that may precipitate or "trigger" disruption.

Following disruption, haemorrhage into the plaque, luminal thrombosis, embolization of thrombotic material and/or vasospasm may cause sudden flow obstruction, giving rise to new or changing symptoms. The culprit lesion is frequently "dynamic", causing intermittent flow obstruction, and clinical presentation and outcome depend on the severity and duration of myocardial ischemia[5,12] The challenge is to identify and treat the dangerous vulnerable plaques responsible for the life-threatening ACS. To remove the angina–producing stenotic lesions is not enough. Culprit lesion-based interventions usually eliminate anginal pain, but do not substantially improve the long–term outcome. MI and death depend more on co-existing non-symptomatic vulnerable plaque than on stenotic angina-producing lesions[13]

Definitions and clinical manifestations

Acute MI is defined as myocardial necrosis secondary to interruption of coronary blood supply. However, as these findings can only be confirmed histologically, the clinical diagnosis is based on the history, ECG findings and elevated biochemical markers indicating myocardial

damage. Modern classification of MI differentiates between ST elevation MI (STEMI) and non ST- elevation MI (non STEMI). STEMI usually develops secondary to a thrombotic and persistent occlusion of a coronary artery, not compensated by collateral flow[14]. Non STEMI is mostly caused by coronary thrombus associated either with subtotal or transient short-lasting occlusions or downstream embolization or with persistent total occlusion, where preformed collaterals protect the jeopardized myocardium[15]. Unstable angina pectoris (UAP) is a clinical syndrome characterised by sudden worsening of a previously stable angina, new-onset severe angina, or angina at rest[16, 7].

In this heterogeneous spectrum, both high risk patients with ST depression or T-wave inversion on ECG and /or minor elevation of biochemical markers not fulfilling the MI criteria and low risk patients without ECG changes indicating ischemia and no biochemical evidence of myocardial necrosis, can be identified. Due to a similar pathophysiology with often severe coronary artery lesions, a new formed thrombus obstructing the blood supply and high risk of new thrombotic events UAP and non STEMI are often put together into one entity as if these two conditions were more or less the same[18,19] In the year 2000, new guidelines on MI definition were introduced[20].

Consequently, a substantial number of patients previously diagnosed with UAP, today fulfil the criteria for MI.

Quality of life in coronary artery disease

Despite advances in treatment and preventive measures, ischemic heart disease is still imposing a considerable burden on the individual and on society. Morbidity after ACS includes both physical and mental disorders influencing the patient's entire life situation and affects his/her quality of life (QoL)[21,22] Lately, it has been increasingly common to include assessment of QoL in trials of CAD. Measurements of QoL are aimed to capture the patient's own experience of health and illness in a broad perspective. The recognition that the patients' own perception of his/her health status may be as interesting as the standard clinical end-points is a new way of thinking in modern healthcare. A person's perception of health and satisfaction with life is very much affected by his or her expectations regarding health and ability to coupe with limitations and disability. For many patients with ischemic heart disease the ability to function in daily life, both physically and mentally is important. Feeling of well-being and to be able to participate in social life is also important and perceived cognitive function reflecting how to concentrate, activity drive, memory and problem-solving, has a major impact on QoL[23].

Gender perspectives in coronary artery disease.

The relatively low frequency of ACS in women as compared to men was first described by Heberden in the early 19th century. He described women to have a "protective factor" against coronary artery disease. In those days, women reached the age of 50 years, thus never entering menopause. Clearly, the relatively higher occurrence of ACS in men has during decades tended to undermine the importance of ACS as reason for morbidity and mortality in women. Today, ACS is the leading cause of death in both gender of the western world and during the last two decades there has been an ongoing debate about women and ACS and whether women and men suffering from this syndrome differ in baseline characteristics, clinical presentation, treatment and outcome[24-27]. Early mortality among patients hospitalized with an acute MI has been consistently reported to be higher among women than men[28,29]. An important question has been whether women tend to be treated less vigorously than men although current knowledge from a couple of studies strongly indicates that women in

most aspects benefit as much as men from recommended therapies[30,31]. In contrast to these studies, FRISC II and RITA 3 trials reported worsening outcomes among women with ACS who were treated invasively. This finding has raised doubt as to whether treatment in women and men should be similar[32,33].

Among studies investigating the association between sex, age and early mortality, results differ from no association[24,34], to worse prognosis in older women only[35] or surprisingly worse prognosis only in younger women[27,36]. The higher short-term mortality among older women is explained by older age alone or in combination with a higher frequency of co-morbidities and a more complicated clinical course[37]. However, findings from the American National Registry of MI support a worse in-hospital mortality among younger but not older women with a linear increase in risk with decreasing age[27]. From our Swedish MI registry, Rosengren et al. reported in 2001 a higher in-hospital mortality among women below 70 years of age[36] The reasons for the sex-age differences in early mortality remain unclear, although Vaccarino *et al.* explained in 1999 that younger, but not older women hospitalized with MI, suffered from more diabetes and congestive heart failure, as reason for worse short-term outcome among younger women[27]. Another possible explanation is gender differences in the management after MI[38].

Reperfusion and other medically proven therapies used at the acute phase are less often used in both older and younger women compared with men. Moreover the higher rates of in-hospital deaths among younger women might be balanced with a higher rate of pre-hospital deaths in men[39].

In contrast to studies on short-term mortality, several studies examining long-term outcome among survivors after the acute phase, did not differ in mortality between women and men[40,41] and some even found a more favourable outcome in women. The more favourable long-term outcome in women as compared with men, could be explained to some extent by the different life-expectancy of women and men[42]. Women may appear to have a similar or even better long-term outcome due to underlying survival advantage[43].

Other studies investigating age-sex differences in long-term mortality beyond the hospital stay support higher long-term mortality rates among women, particularly younger women, compared with men at same ages. In a study from 2001, Vaccarino *et al* observed that women younger than 60 years of age had a higher mortality rate than men and the mortality risk for women compared with men decreased by increasing age, to the point where women in the oldest age groups showed a lower 2 year mortality rate than men of similar age[36,44].

Age perspectives in coronary artery disease

Clinical characteristics, treatment and outcome in patients with ACS differ not only due to gender but also between various age groups. Older individuals make the fastest–growing segment of the population in the western countries. CAD is highly prevalent and accounts for the majority of deaths in elderly people[45]. Thus they constitute an increasing percentage of patients admitted to hospitals for ACS and are a high risk population for which physicians and healthcare systems most probably should provide the same evidence-based ACS therapy as in younger generations. Paradoxically, studies show trends toward underutilization of such therapy in the elderly[46]. The lack of evidence to guide treatment compounded by the high prevalence of co-morbidities among elderly may partly explain the under use of medical and interventional therapies in this population[47,48]. The underutilization of evidence-based cardiac therapies and higher mortality in older patients, reported from several studies, is increasing in each successive age group[47].

Thus, the practice of grouping older patients, i.e. patients >65 years, together as a single age group may obscure important age-associated differences. There are considerable differences as to management and outcome in patients with ACS <65 years and >75 years[37, 49].

Some authors have suggested that elderly with MI do not benefit and may even be harmed by thrombolysis[50]. In contrast, Stenestrand *et al* reported in 2003 from the Swedish RIKS-HIA, that fibrinolytic therapy in patients with STEMI, 75 years and older, was associated with a reduction in the composite of mortality and cerebral bleedings after 1 year[51]. Moreover, the beneficial effects of other pharmacologic therapies such as beta-blockers and statins have been shown to extend to the elderly patients[52,53]. The fact that elderly patients may not receive optimal treatment for ACS, despite the availability of proven, scientific evidence, emphasize the need for ongoing research to optimize therapeutic regimens and adherence for the rapidly growing elderly population at high risk.

Management and treatment

The treatment of patients suffering from ACS has changed dramatically during the last two decades. Prompt and effective reperfusion therapy, using thrombolysis or preferably primary percutaneous coronary intervention (PCI), is the cornerstone in the management of STEMI[54,55]. Non STEMI and UAP are more heterogeneous groups, which in clinical practice has led to a greater variation in diagnosis and treatment. For non STEMI ACS, expert guidelines today recommend early risk stratification, effective antithrombotic therapy and a low threshold for angiography especially in high risk patients[18,56]. As to adjunctive therapy, current guidelines for STEMI and non STEMI ACS are more or less the same with beta-blockers, angiotensin converting enzymes (ACE) inhibitors, antiplatelet agents and statins included in the therapeutic strategy for most patients already in the acute phase. The long-term treatment is, irrespective of type of syndrome, based on an aggressive risk factor modification.

To stop smoking is crucial, hypertension and hyperglycaemia should be treated and cholesterol lowered. Beta-blockers improve prognosis and ought to be prescribed to all patients with an episode of ACS. Lipid lowering therapy should be initiated as soon as possible. Statins are known to reduce morbidity and mortality in women and men with CAD. Beside the improvements on the lipid profile, the statins seem to stimulate the endothelial function and reduce the inflammatory response of the plaque. In a study from 2000, Ysuf *et al*. showed beneficial risk-reducing effects of ACE inhibitors on morbidity and mortality in patients with CAD[57]. Thus, ACE inhibitors should be prescribed to all patients with CAD and to all patients with left ventricular dys-function irrespective of origin.

In spite of these advances in management of ACS, the rate of cardiovascular mortality after discharge in still high.

Prognosis

With many therapeutic options available the clinician is challenged to identity type of syndrome, make an early risk factor assessment and offer the safest and most effective treatment for survival of each individual patient.

Data regarding prognosis in populations covering the whole spectrum of ACS are scarce. Considerable variability exists in risk for adverse events across the whole spectrum of ACS. Difference in clinical characteristics at presentation identified as varying risk variables, are now important factors in deciding on the level of care and choice of interventional and medical therapies[58,59]. Current guidelines from the American College of Cardiology/ American Heart Association and the European Society of Cardiology[56] recommend certain pharmacological and

interventional strategies as standard therapy in high-risk patients. A number of multivariable prognostic models have been developed in populations of patients with STEMI[60,61] and with non-STEMI ACS[58,62,63]. Most of these models are derived from databases in clinical trials leading to some of the most powerful predictors on mortality developed in the selected population of patients with STEMI treated with thrombolytics and consequently not relevant in all cardiac patients[61,64]. In 2003, the multinational, observational Global Registry of Acute Coronary Events (GRACE) developed, in order to determine factors predictive of death across the entire spectrum of ACS, a multivariable, prognostic model. A few variables were found to be consistent, powerful predictors of risk for hospital mortality in ACS. These were Killip class, age, blood pressure, cardiac arrest, positive findings for biochemical markers, creatinine level, ST-segment shift and heart rate[65].

It is important to realize that variables predictive of a poorer short-term outcome following ACS are not necessarily those of most importance for the long-term outcome and vice versa.

Long-term prognosis of ACS survivors varies substantially according to conventional risk factor profile. Risk stratification for these patients is rather scarce. Factors identified from prior studies to be predictive of death in the long run include demographics (age and gender), predisposing conditions and behaviours (diabetes mellitus, hypertension and smoking) and prior cardiovascular events (stroke, previous MI)[66]. Other authors emphasize the prognostic value of baseline renal dysfunction in patients with ACS. Renal dysfunction is shown to independently predict higher mortality in patients with ACS[67,68]. The under-utilization of reperfusion therapy in patients with renal dysfunction may contribute to the poor outcome

Diabetes mellitus is a major contributor to CAD and associated with substantially increased mortality and morbidity[69]. Recent evidence support early revascularization in high-risk ACS patients. Diabetic patients subjected to coronary interventions are known to have a higher risk for complications and poorer prognosis than non-diabetic subjects. Although diabetes remained an independent and important risk factor for death, Norhammar et al showed in a study from 2004, that an invasive strategy improved 1 year outcome for both diabetic and non-diabetic patients with unstable angina pectoris[70].

Smoking is a risk factor for chronic CAD and also known to strongly predict a poorer long-term outcome after ACS. A paradoxical survival advantage to current or prior cigarette smoking in patients admitted with ACS has been observed. The GRACE investigators clearly demonstrated in 2005 that the smokers' paradox does not exist; there are no beneficial effects in smokers with ACS[71,72].

AIMS OF THE PRESENT STUDY

In this prospective study of consecutive "real life" patients < 80 years of age with different types of acute coronary syndromes, treated in a coronary care unit, the following aims were selected for the present thesis:

- To study gender differences in baseline characteristics, clinical presentation and treatment in relation to age and type of syndrome.

- To study gender differences in terms of short- and long-term morbidity and mortality and to identify factors predictive of late death among women and men surviving the acute phase of an acute coronary syndrome.

- To analyse whether there are similarities and differences in risk factors, previous history, clinical presentation, management, complications and short-term and long-term outcome in patients with different types of the syndrome.

- To evaluate whether elderly patients are managed differently from younger ones and to examine differences in morbidity and mortality in relation to age

- To study quality of life at a 3-month follow-up in patients with acute coronary syndromes, with the main objective of exploring whether unstable angina pectoris and myocardial infarction patients differ in this respect.

MATERIALS AND METHODS

Study population

Patients admitted to the coronary care unit (CCU) of Sahlgrenska University Hospital, Göteborg, Sweden between Sept 15, 1995 and Sept 15, 1999 with suspicion of ACS, were evaluated for participation in a study on prognosis and its prediction in ACS in real life (PRACSIS = Prognosis and Risk of Acute Coronary Syndromes in Sweden). Our hospital serves half of the 450.000 inhabitants of the city of Göteborg and is also a tertiary centre for the Western Health Care Region of Sweden with 1.5 million inhabitants. To enable long-term follow-up only patients under the age of 80 and living within the hospital's catchment area were eligible for the study. Patients transferred from other hospitals for tertiary care were not included, nor were patients with ACS treated outside the CCU. The study was approved by the ethics committee of Göteborg University.

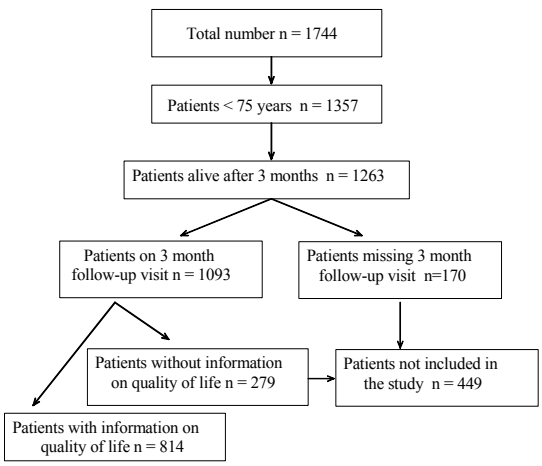
The suspicion of ACS had to be supported by ECG changes on admission (ST elevation ≥0.1mV (0,2 mV in V1-V4) or ST depression ≥0.1mV or T wave inversion in at least two adjacent leads), biochemical markers above the upper reference level (creatine-kinase (CK)-MB 5µg/l and/or troponin T 0.05 µg/l), or previously recognized coronary artery disease, such as MI, prior PCI or coronary artery bypass grafting (CABG), stable or unstable angina pectoris with significant angiographic changes, or an exercise test suggestive of ischemia . The exclusion criteria were severe non- cardiac disease with expected survival less and 1 year, and unwillingness to participate. A patient could only be included once.

Only 8 eligible patients fulfilled the exclusion criteria. A further 29 with UAP and 52 with acute MI were missed for logistic reasons. In all 1,854 patients were enrolled in the study. Among these 110 were finally discharged with a diagnosis other than UAP or MI despite an initial strong suspicion of an ACS.

This thesis deals with the 1,744 patients (546 women and 1198 men) with a definite diagnosis of UAP or acute MI. They were retrospectively divided into four groups in assumed decreasing order of severity based on ECG and biochemical markers of myocardial ischemia and necrosis (1) STEMI with ST segment elevation or left bundle branch block and CK-MB >10 µg/l and/or troponin T ≥0.15 µg/l, n= 622; (2) non-STEMI with CK-MB >10 µg/l and/or troponin T ≥015ug/l, n=594; (3) high-risk UAP with ST depression ≥0,1mV or T- wave inversion and/or CK-MB 5-10 µg/l and/or troponin T 0.05-0.14 µg/, n=226; and (4) low-risk UAP with typical symptoms but without ECG changes indicating acute ischemia and CK-MB ≤5µg/l and troponin T <0.05 µg/l, n=302. The patients were also divided into three groups according to age: <65 years, 65-74 years, and 75-79 years.

In Paper 3, only patients below the age of 75, who accepted an invitation to follow-up visit at the out-patient clinic 3 months after discharge were eligible for participation. The flow of patients is illustrated in Fig. 1. In this paper the two main groups, UAP or MI, were created on the basis of hospital discharge diagnosis.

Figure 1



Data collection

Data were collected from the hospital medical records, including information on previous clinical history, risk factors and medication. While hospitalized, the study patients also passed a detailed interview conducted by an experienced study nurse. The time for onset of symptoms, the delay times, clinical presentation and ECG appearance on arrival, as well as ECG changes during the hospital stay were registered. Twelve lead ECG recordings at 50 mm/s were used. Diabetes was defined as a previously known diabetes mellitus. Similarly, hypertension and hyper-cholesterolemia were defined as previously known disorders and revealed by interview or registered in previous hospital records.

The research nurse registered height and weight. Body mass index (BMI) was calculated as (body weight, kg)/ (height, m^2). During the hospital stay, detailed surveys of the most important complications, medical treatment and investigations were made. At discharge, medical treatment, planned investigations and revascularization procedures, as well as the time spent in hospital, were documented. In- hospital mortality and mortality within 30 days were recorded. Information on deaths within five years as well as survival confirmation at five years was obtained from the Swedish National Population Register. Information on cause of death and readmission to hospital were obtained from the Swedish Cause of Death Register and the Swedish Hospital Discharge Register and was available for 45 months follow-up for all patients. Short-term mortality was defined as deaths within 30 days and late long-term mortality as death between 30 days and 5 years.

Quality of Life Instrument (paper 3)

The Cardiac Health Profile (CHP) a disease-specific questionnaire for assessing health-related QoL, was used. It has been developed, tested and found to be reliable, valid and sensitive in a Swedish population with cardiovascular disease. The questionnaire consists of three parts. Part 1 assesses the self-reported degree of angina pectoris according to the modified CCS classification. The second part assesses health- related QoL in a broad perspective and consists of 16 questions including physical function/general health, social function, emotional function and cognitive function. Part 3 deals with patients who have had interventional treatment in one way or another and was not applicable to our study. The CHP results can be analyzed per item, as the four independent domains or as a total score. In this study we focused on the global mean score (GMS), but we have also looked separately at the scores in the four domains. The 16 items and four domains in the English version of the questionnaire are shown in Appendix 1.

General comments

The present study was conducted in a coronary care unit at a University Hospital with catheterization laboratories and cardiac surgery facilities in the second largest city of Sweden. People dying outside hospital were for obvious reasons not included, which means that more men than women were lost from participation at this very early stage[39].

Our hospital's catchment area is half of the inhabitants in Gothenburg, thus a strictly urban population from areas with slightly better socioeconomic circumstances than the other half of the city. We can therefore not exclude a survival advantage in our patients compared to the total Gothenburg ACS population[73]. No octogenarians participated in the study. The findings we did in our highest age group, with an increasing number of women and patients with non ST-elevation MI, would therefore have been further strengthened if no upper age limit had been set[74,75]. We know from previous studies at our hospital, that 20-25% of patients with ACS below 80 are treated in internal medicine wards[76]. An analysis of these patients from 1998 showed a somewhat

higher proportion of females than in our study (39% vs. 31%) and a higher proportion of non STEMI. (unpublished data). They were with very few exceptions not subjected to invasive procedures.

In order to provide data on the entire spectrum of ACS, the GRACE project was designed some years ago. With a similar goal two Euro Heart Surveys on ACS have been conducted[74,75]. An interesting finding is that our ACS population is slightly older in spite of our upper age limit of 80 years, the percentage of women is similar or higher, and our mortality is higher than what has been presented from these projects. This indicates that we in spite of the limitations above in comparison with other similar reports have a satisfactory representation of the spectrum of ACS.

In comparison with studies on ACS from national registries we have the advantage of higher quality on our data. One experienced study nurse made all the interviews and collected data from the hospital medical records. If information obtained from these interviews differed from those in the medical records a thorough work-up was done to resolve the discrepancies

Our study was conducted before the new guidelines on infarct definition were introduced. During the entire study period serial measurements of CK-MB was the routine method for MI diagnosis at the hospital. Although additional measurement of troponin-T was recommended for the patients participating in the study, data turned out to be missing in a fairly high proportion of patients. This means that no retrospective subdivision of patients according to modern diagnostic criteria have been possible. Obviously some patients in our high risk UAP group would today have been diagnosed with non STEMI.

There have been great advances in the management and care of ACS patients during recent years. One could argue that our data are fairly old and therefore not relevant for ACS patients of today. However, the frequencies of coronary angiographies as well as revascularization procedures were quite high in our study and well comparable with more recent figures from studies on ACS[77].

STATISTICS

In Paper 1 and 2, age-adjusted p-values were calculated using logistic regression for dichotomous variables and Spearman's partial rank correlation for ordered/continuous variables. To test for associations with severity of ACS and with ordered age groups, Mantel-Haentszel's chi-square test was used. ACS was regarded as an ordered variable with decreasing severity from ST-elevation MI to low-risk type unstable angina. Interactions were tested using logistic regression models.

For the univariate analysis in Paper 3, the association with CHP score was tested using the Mann-Whitney U test for dichotomous variables and Spearman's rank statistics for continuous variables. Group comparisons of characteristics, clinical course, treatment and medication were made using Fischer's exact test for proportions and the Mann-Whitney U-test for age and length of hospital stay.

Multivariate analyses were performed using a logistic regression model, in which the CHP-scores of all 814 patients were divided into quartiles (i.e. by the 25th, 50th and 75th percentiles, which corresponded to a CHP score of 20, 32 and 46 respectively) as an ordinal four-graded response variable.

In Paper 4, Kaplain-Meier estimates were used and tests were performed using the log rank rest. Cox proportional hazard model was used for adjusted comparisons, hazard ratio cacluclations (adjusted as well as unadjusted) and for identification of predictors of late long-term mortality.

All p-values are two-tailed and considered significant if below 0.01 in paper 1 and 2 and below 0.05 in paper 3 and 4.

Observations in Relation to Gender

Baseline

Among the 1744 patients with ACS, 31% were women. Whilst the proportions of STEMI did not differ between genders, non STEMI was more common in men and UAP in women (Fig. 2).

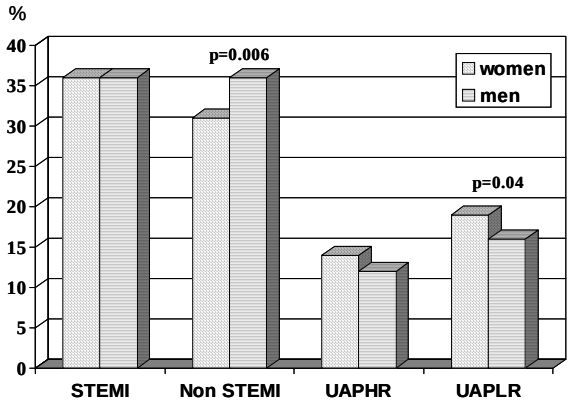


Figure 2. Type of syndrome in relation to gender

The frequency of diabetes was similar in women and men, as was the frequency of previous PCI. More than 50% of both genders were overweight. Regarding medication, at entry men were more often on aspirin whereas a higher proportion of women was treated with diuretics. Women delayed seeking medical care longer than men and had more often a longer stay in the emergency department. At entry women more often tended to present with normal ECG while right bundle branch block was more common in men as was a pathological ECG without signs of an acute ischemia (Fig. 3).

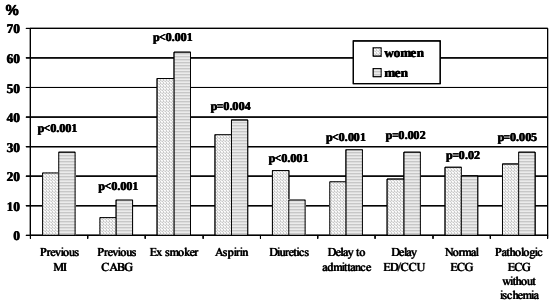


Figure 3. Baseline characteristics, delay and ECG at presentation in relation to gender

In Hospital - 30 days

Reperfusion therapy was given to 65% of the 194 women and 72% of the 428 men (p=0.50, age adjusted) with STEMI (Fig. 4).

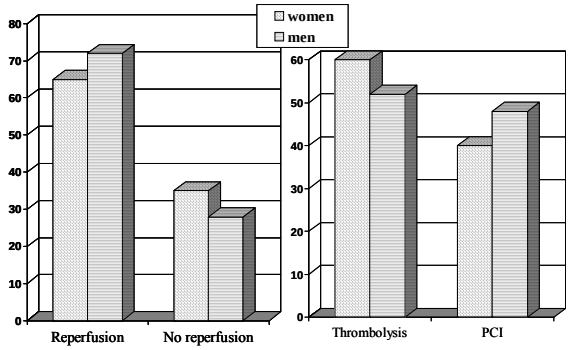


Figure 4. Reperfusion therapy among STEMI patients in relation to gender

PCI was used in 40% of the women and 48% of the men (p=0.83, age adjusted). There were no significant gender differences with respect to in-hospital complications and all medical therapy was used in a similar frequency in women and men. Women were less likely to be scheduled for CABG after discharge while the use of PCI showed no gender differences. A tendency towards a somewhat more frequent use of diuretics at discharge in women was seen while beta-blockers, ACE inhibitors, lipid lowering agents and aspirin were, in similar frequency prescribed to women and men (Figs 5 and 6).

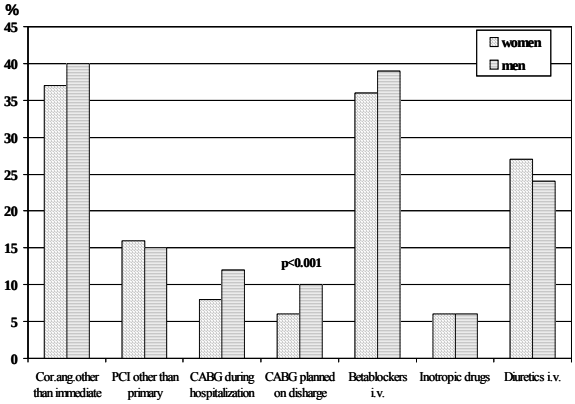


Figure 5. In-hospital treatment in relation to gender

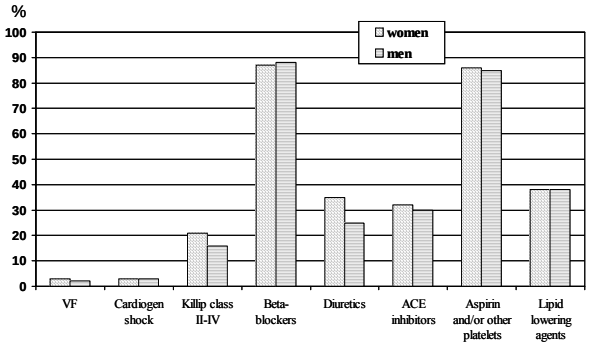


Figure 6. Complications and discharge medication in relation to gender

The short-term mortality did not differ between women and men; 6.4 versus 5.8 (p=0.62) in-hospital and 8.2 versus 6.8 (p=0.85) at 30 days, respectively. Six variables independently predictive of short-term mortality were identified. These were age, blood pressure <100mmHg, Killip class >I, cardiac arrest prior to admission, elevated creatinine levels at entry and atrial fibrillation. No significant gender differences were observed.

Long-term follow-up

The late (>30 days) five year mortality was 21.0% for women and 18.2% for men. After adjusting for age differences, the HR and corresponding 95% CI for a higher late five year mortality in women in relation to men, was 0.89 (0.70,1.13), p=0.34.

Cardiovascular morbidity and mortality during 45 months are shown in Fig. 7. Before, but not after, adjustment for age there was a significant gender difference in readmission for congestive heart failure (CHF), p=0.005 and p=0.23, respectively. Neither unadjusted nor adjusted for age did women nor men differ significantly in terms of readmission for MI, revascularization or cardiovascular mortality.

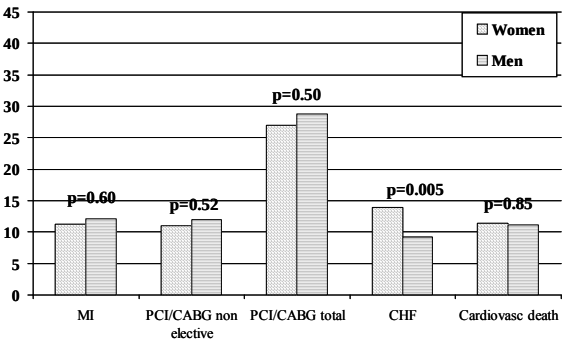
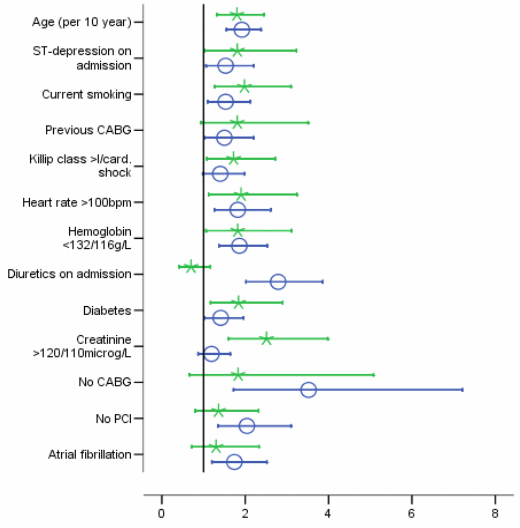


Figure 7. Cardiovascular death and readmission to hospital during 45-month follow-up in relation to gender

Thirteen variables related to baseline characteristics and hospital course were identified as factors with a significant influence on late mortality in the whole group of patients. Of these, age, ST-depression on admission, diabetes, current smoking, heart rate >100 on admission and a haemoglobin level below the normal limit were significant predictors of death in both gender. Previous CABG was significantly associated with death in men, as were atrial fibrillation, PCI and CABG during hospitalization, with a clear trend for previous CABG also in women. The situation was the other way around for cardiogenic shock/Killip class >I, i.e. significance in women and a trend in the same direction in men. Except for two variables there was no interaction between gender and factor, regarding mortality. These two were previous treatment with diuretics, which had a larger impact on prognosis in men, and a creatinine value on admission above normal upper limit, which showed a more marked importance in women.(Fig.8)(*=women, Θ=men).



Observations in Relation to Type of ACS

Baseline

A less severe type of ACS, UAP instead of MI, was associated with a higher prevalence of previous MI, angina, CABG and PCI, a progressing angina prior to admission, a history of hypercholestero-

lemia, past smoking, ongoing treatment with beta-blockers, aspirin, lipid lowering agents, long-acting nitrates, calcium blockers or diuretics, admittance via emergency ward instead of direct to CCU, and a normal ECG on admission. There was no significant interaction between sex, severity of the syndrome and the studied variables (Fig. 9).

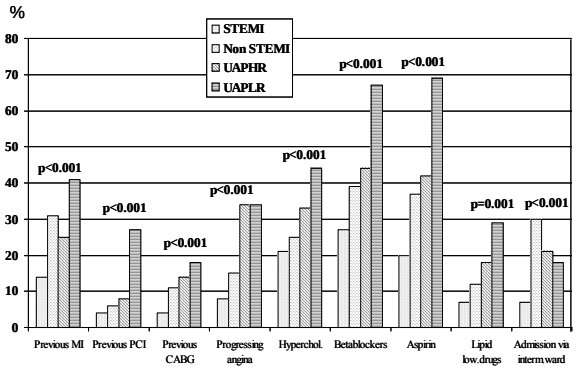


Figure 9. Baseline characteristics in relation to type of acute coronary syndrome

In hospital - 30 days - 5 years

In hospital complications were associated with the more severe type of ACS, MI instead of UAP. In contrast, all coronary interventions, other than primary PCI, were performed more frequently the less critically ill the patients were (Fig. 10).

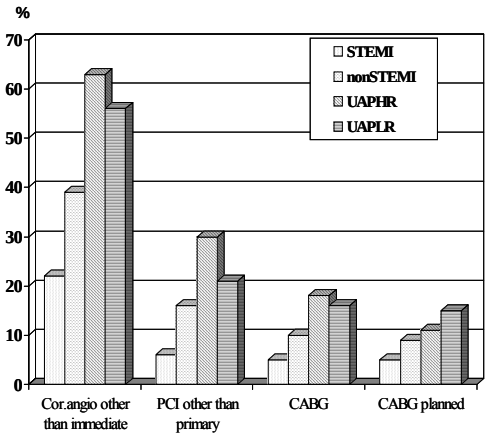


Figure 10. In-hospital investigations in relation to type of acute coronary syndrome

Treatment with ACE inhibitors at discharge was the only prescribed drug with a significant relation to severity of disease (Fig. 11). The 30 day mortality was nearly twice as high in STEMI patients, compared with patients with non STEMI (12,4% versus 7,4%, p=0.004). The 30-day mortality was considerably lower in patients with UAP and did not differ much between the two groups (Figs. 11, 12).

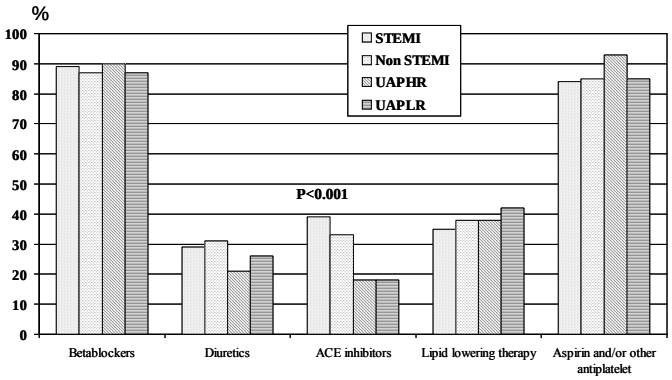


Figure 11. Discharge medication in relation to type of acute coronary syndrome

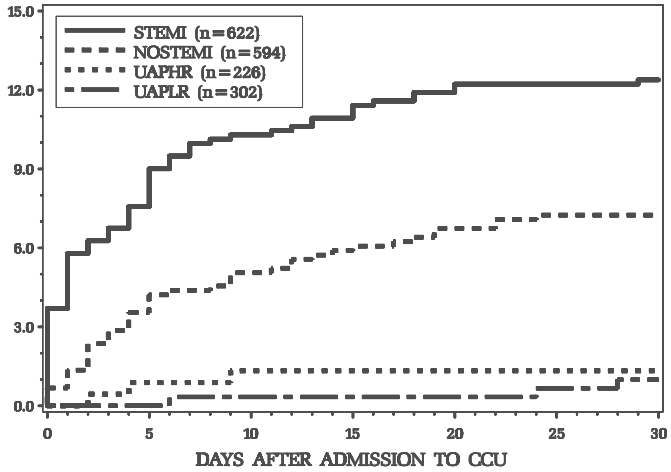


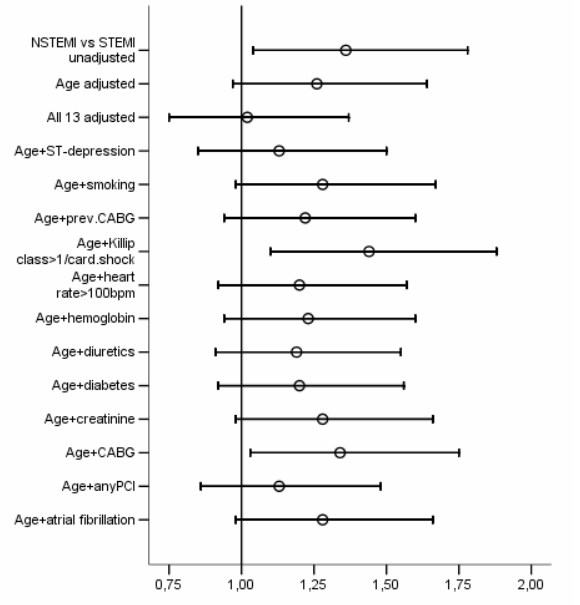
Figure 12. Short-term mortality in relation to type of acute coronary syndrome

There was no interaction between gender and type of syndrome regarding mortality. Non STEMI patients had higher late 5 year mortality than the other categories, 24%.

Survival in STEMI and UAP high risk patients were surprisingly similar (18% and 16%, respectively) with the lowest 5 year mortality in UAP low risk (13%). HR with 95% CI for late 5 year mortality in the three other types of ACS in comparison with UAP low risk after adjustment for age was 1.66 (1.16-2.38) for non STEMI, 1.31 (0.90-1.90) for STEMI and 1.20 (0.77-1.89) for UAP high risk. After adjustment for all 13 clinical variables with impact on prognosis as previously described the HR for non STEMI versus UAP low risk was 1.21 (0.80-1.81). When a comparison between non STEMI and STEMI was carried out with adjustment for age in

combination with each of the 12 prognostic factors (including all patients without missing data), one at a time, the largest influence on HR was seen from Killip class on admission, adjustment for which led to a larger difference in mortality between non STEMI and STEMI.

The two variables responsible for the largest decrease in HR, i.e. diminished mortality difference between groups, were ST-depression on ECG on admission and revascularization with PCI (HR and 95% CI unadjusted 1.36 [1.04-1.78], p=0.02, adjusted for age 1.26 [0.97-1.54], p=0.08 and adjusted for all thirteen variables 1.02 [0.75-1.37], p=0.92) Fig. 13.



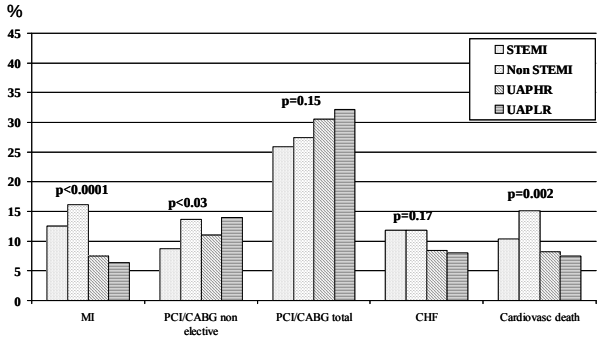


Figure 14. Cardiovascular death and readmission to hospital during 45-month follow-up in relation to type syndrome

Cardiovascular morbidity and mortality during 45 months are shown in Fig. 14. There was an overall significant relationship between type of syndrome and readmission for MI (p<0.0001), non elective revascularization (p=0.03) and cardiovascular mortality (p=0.002). A comparison between non STEMI and STEMI yielded HR and 95% CI of 1.61 (1.11-2.33) for non elective revascularization (p=0.01) during 45 months after adjustment for age. There was no significant difference between non STEMI and STEMI with respect to readmission for MI, total revascularization and hospital readmission due to CHF. There was a trend for difference in cardiovascular mortality (HR 1.50 [1.07-2.10], p=0.02 unadjusted and HR 1.38 [0.98-1.93], p=0.07) after adjustment for age.

Observations in Relation to Age

Baseline

An older age was associated with female sex, non STEMI, a history of cardiac diseases and ongoing treatments with cardiac drugs. Ambulance use, heart rate >100 bpm, Killip class II-IV and right bundle branch block were more common with increasing age. A lower age was associated with UAP low risk, previous PCI, hypercholesterolemia, current smoking and normal ECG on admission (Fig. 15).

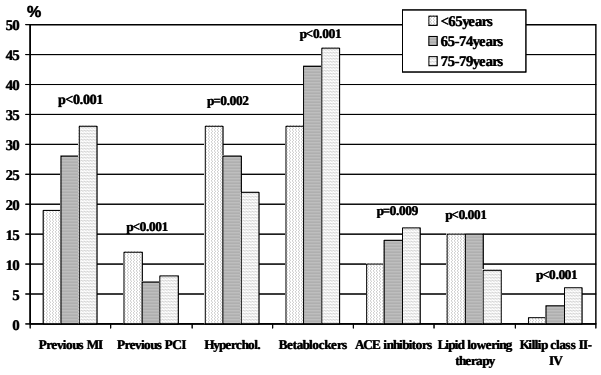


Figure 15. Baseline characteristics and clinical features in relation to age

Diuretic treatment and systolic blood pressure <100 mmHg were more common in younger women than younger men while this difference was absent or even - in the case of systolic blood pressure <100 mmHg-reversed in older patients.

Hypercholesterolemia was more common among older women than older

men, whilst this difference tended to be reversed with a lower age.

In hospital - 30 days - 5 years

Patients with STEMI constituted 36% below 65 years of age, 35% between 65 and 74 years and 36% at age 75–79. In the three age groups, 79%, 70% and 56% of STEMI patients underwent reperfusion therapy. Of all patients who underwent reperfusion therapy, the use of PCI decreased with increasing age; 59%, 39% and 31% in the three age groups, respectively, (p<0.0001) (Fig. 16).

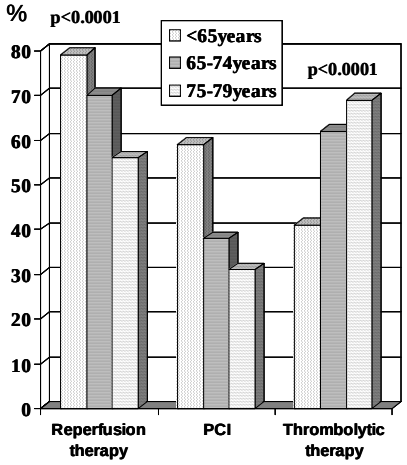


Figure 16. Reperfusion therapy in patient with with STEMI in relation to age

Complications and mortality was associated with increasing age as was length of hospital stay. The lower age group was associated with coronary angiography, PCI during hospitalization and, to a larger extent, lipid lowering, while treatment with diuretics and ACE inhibitors at discharge was more frequent in the higher age group. (Fig. 17,18)

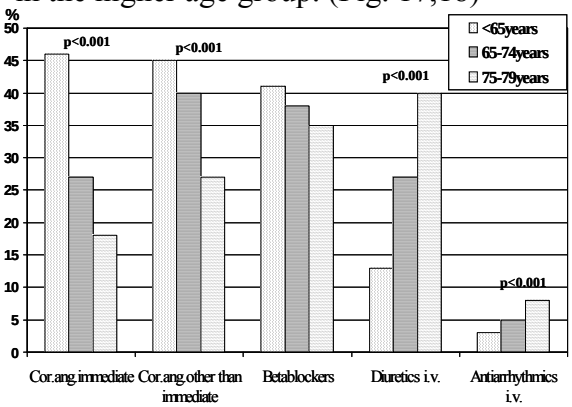


Figure 17. In-hospital treatment and investigations in relation to age

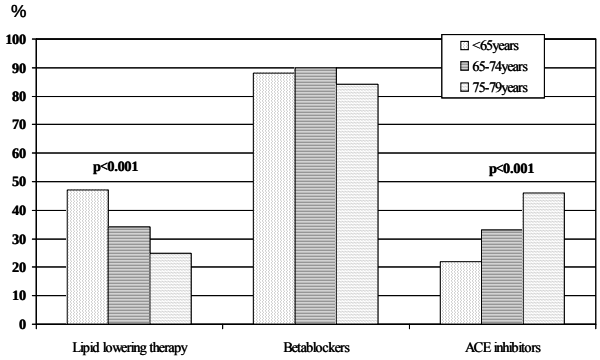


Figure 18. Medication at discharge in relation to age

The use of Warfarin and/or aspirin/ antiplatelets at discharge was lower among younger women than among younger men (p<0.0001), whilst this difference reversed with increasing age. The situation was opposite for diuretics, with a higher use among women than men in patients in the lower age group (p<0.0001), but lower among older group. The 30-day mortality was similar among women and men in each of the three age groups. Late mortality increased with age, with no significant differences between women and men to the point that men older than 74 years had a higher mortality than women of similar age (p=0.04) (Fig 19)

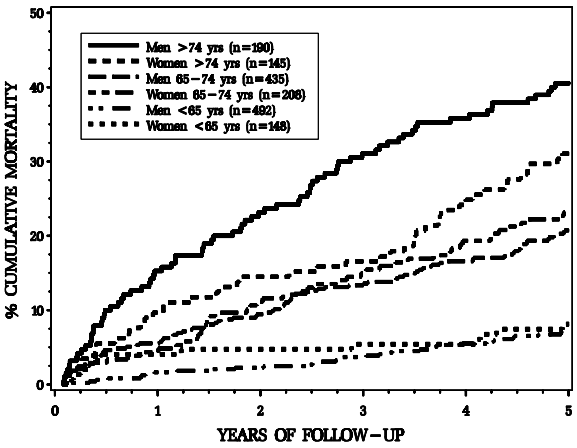


Figure 19. Late (>30 days) five year mortality in women and men in relation to age

Quality of Life

Non-participants

Data from the 814 patients included in the study was compared with data from the 449 patients alive 3 months after index discharge and not attending follow-up and/or answering the questionnaire

correctly. The groups were similar regarding diagnosis, age and gender. Factors associated with poorer QoL were more prevalent in non participants, particularly in patients with UAP.

Characteristics in UAP versus MI

Of 814 patients answering the questionnaire, 278 (34%) were discharged with the diagnosis UAP and 536 (66%) with MI. Current smoking was more common among MI patients as was in-hospital complications, except for recurrent angina. Hypertension, lipid disorder, previous cardiac diseases and interventions were all significantly more frequent in the UAP group. The frequency of revascularization prior to the 3 months follow-up visit (PCI and/or CABG) was similar in the UAP and MI group (54% vs 52%).

CHP in UAP vs MI.

The self-reported degree of angina in Part I of the CHP questionnaire differed between MI and UAP at the 3-month visit with significantly higher percentage of angina in the UAP group ($p<0.0001$). The total QoL scores (Part II of the questionnaire) at the 3-month follow-up were significantly ($p=0.006$) higher for the patients with UAP (median 34; 22, 50) than for those with MI (median 30; 19, 44), as illustrated in Fig. 20 (left panel).

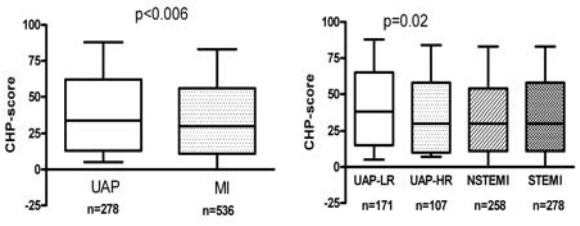


Figure 20. Boxplots describing the global mean score in Cardiac Health Profile at the 3-month follow-up for UAP and MI patients (left) and for patients in four groups with assumed decreasing order of severity (right)

Analyses identifying the four independent domains showed that perceived cognitive function as well as physical function/ general health predicted a poorer QoL in UAP patients as compared to MI at the 3-month follow-up ($p=0.03$ and $p> 0.0001$, respectively)(Fig. 21).

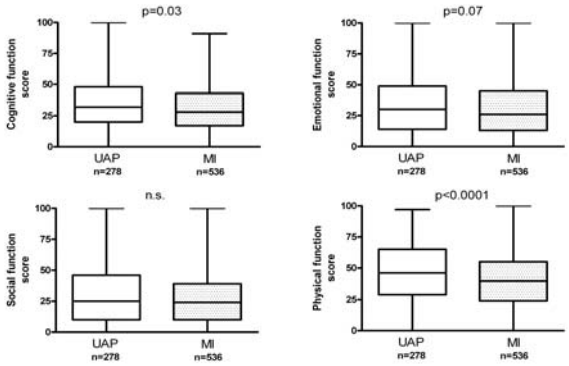


Figure21. Boxplots describing the scores in the four domains at the 3 month follow-up for patients with UAP and MI

After a further subdivision of the ACS patients into four groups with assumed decreasing order of severity, patients with UAP of the low-risk type reported significantly more angina than the others (Part 1 of the questionnaire). The low-risk group had a median total QoL score of 38 (24,52) vs 30 (16,44) for patients with high-risk UAP ($p<0.002$, Fig. 20, right panel). A median QoL score of 30 was seen in both types of MI patients.

QoL in Relation to Characteristics of ACS Patients

Characteristics significantly associated with poor QoL included female sex, lower age, current smoking, hypertension, diabetes mellitus, a history of angina pectoris, previous MI, previous CABG, hospitalization for proven or suspected cardiac disease during the preceding year, heart failure, pulmonary disease, intermittent claudication, other chronic disease and treatment with sedatives and antidepressants. Patients who had been subjected to CABG prior to the 3-month visit had a better QoL than patients who did not undergo heart surgery. Recurrent angina, ongoing treatment with antidiabetics, long-acting nitrates and sedatives/antidepressants were associated with a poorer QoL.

Multivariable Analysis of CHP in UAP vs. MI

The uppermost line in Fig. 22 represents the unadjusted odds ratios and corresponding 95% confidence intervals for a poorer QoL in UAP vs. MI patients.

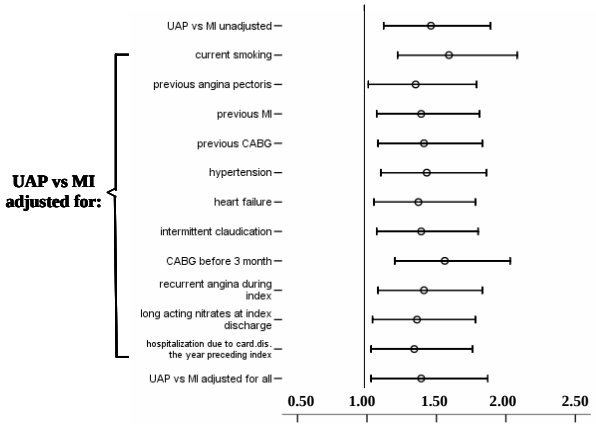


Figure 22. Influence of clinical variables on the difference in quality of life between UAP and MI patients

Below this, there are eleven lines representing the odds ratios for UAP vs. MI patients, separately adjusted for each of the variables which significantly differed between the UAP and MI groups and significantly correlated to CHP scores. Finally, the bottom line represents the UAP vs. MI patients' difference when simultaneously adjusting for all the eleven variables, given odds ratio of 1.39, 95% CI:1.03–1.87, p=0.03 for a poorer QoL in UAP.

DISCUSSION

The overall aim of the PRACSIS (Prognosis and Risk in Acute Coronary Syndromes in Sweden) study was to study prognosis and its predictors in a consecutive series of patients with ACS. This thesis focused on the clinical aspects of ACS and intends to carefully describe clinical features and short-and long-term morbidity and mortality of participants.

Findings in Relation to Gender

Traditionally CAD has been considered a disease predominantly affecting men. For a long time women were not included in cardiovascular research programmes at all. Although the life-time risk of CAD is one in three among women, they are still not fully aware of their risk and perceive the chance of dying from breast cancer as far more likely than from CAD.

In the early 90´s greater attention was focused on women with CAD and since then an increasing number of studies have been published concerning women's cardiovascular health. There is an ongoing debate whether women and men differ in baseline characteristics, as to use of medically proven therapies and revascularization procedures and in outcome after ACS[24-27].

On the whole, the differences we could demonstrate were smaller than expected. An important finding in our study was that early management strategies including reperfusion therapy, coronary angiographies and medical treatment in the acute phase seemed to be quite similar in women and men. However, out of the patients treated with reperfusion therapy, a tendency, although not significant, was observed where men to a larger extent achieved PCI as first preferred choice. The only significant gender difference regarding treatment was CABG planned on discharge which was more common in men. This finding is most probably reflecting less severe CAD in women as suggested in a number of previous studies and also observed by us when comparing the extension of coronary atherosclerosis in our women and men with non STEMI ACS who were subjected to coronary angiography (unpublished data)[33,78]. The women in the present study delayed seeking medical care longer than men and they had longer stays at the emergency department before transmission to the CCU. This is consistent with earlier studies[79]. Women's cardiac symptoms are taken less seriously not only by doctors and other health care workers, but also by the women themselves. The women's denial and dissimilation of the disease might be one reason for these findings[80]. The fact that women in our study presented with STEMI as often as men is not in accordance with previous studies[81]. A possible explanation to our finding is that a female patient with STEMI at our hospital was as likely as a man to be admitted to the CCU, whereas a somewhat higher pro-portion of women than men with non STEMI were treated in medical wards. According to previous studies from our hospital patients with ACS not admitted to the CCU tend to be older and more often women[76,82], Unlike previous reports women in our study did not suffer from more or more severe complications during hospitalization than men and no statistically significant gender–based differences were found in terms of early mortality[24,25]. Studies comparing survival in women and men after ACS, support higher short-term mortality in women.

Differences in baseline clinical characteristics, less use of medically proven therapies and fewer revascularisation procedures have been used as explanation[38]. Another important aspect to consider is that death of a disproportional number of men before hospital admission may represent an inherent gender bias for clinical studies enrolling only hospitalized

patients. Thus, the higher in- hospital mortality among women, may be balanced by the deaths of an equivalent number of men before reaching hospital[36,39,83].

Although most risk factors contribute to CAD in both men and women, the impact of individual risk factors might also be different. Furthermore, variables predictive of a worse short-term outcome following ACS are not necessarily of the same importance for a poorer prognosis long-term and vice versa. We found older age, elevated creatinine, blood pressure <100mmHg, heart failure and cardiac arrest prior to admission as predicative factors of higher early mortality. No significant differences between women and men were observed.

The fact that impaired renal function is predictive of a poor short-term outcome seems to be in line with recent studies emphasizing the prognostic value of baseline renal dysfunction in patients with the entire spectrum of ACS. Goldberg et al found that worsening renal function at admission for STEMI patients is a powerful and independent predictor of in-hospital and one year mortality and suggest that small elevations of serum creatinine may serve as a simple marker to identify patients at a very high risk[67]. Not unexpectedly, signs of hemodynamic instability were associated with higher early mortality in our study. Such signs are important components of all prognostic models for STEMI[61], but lacking in most of the risk scores that have been developed for non STEMI ACS, where ST-depression on ECG and elevated troponins seem to be of greater importance[65,84,85]. Models for the entire spectrum of ACS are scares. However, the GRACE registry score was created from a population like ours and also includes indices of hemodynamic instability, and in addition, in agreement with our findings, prehospital cardiac arrest[65].

In the present study there were no significant gender differences in terms of five- year mortality for patients in the younger age groups, but the mortality risk for men compared with women increased with increasing age, to a point that men older than 74 years had a significant higher long-term mortality than women of a similar age. Most studies on gender differences in long- term outcome among survivors of the acute phase, have found either no differences in mortality between women and men or even more favourable outcome in women[40,41]. The more favourable long-term outcome in women as compared with men could be explained by women' underlying survival advantage. The fact that women are affected with CAD later in life and are supposed to have a less severe disease than men, may contribute to the lower incidence and mortality from MI in women throughout life[43].

As already pointed out, it is of great importance to realize that the variables predictive of short-term outcome following ACS are to some extent different from those of most importance for a poorer prognosis long- term. In the present study well-known risk factors for CAD, such as age, diabetes and smoking also turned out to be risk indicators for poor long-term prognosis. In contrast to the fact that smoking does not influence the early outcome it was of great importance in the long run for both women and men in our study. Similarly, diabetes mellitus was a strong predictor for an adverse long-term outcome in both genders. Diabetes mellitus emerges as an important risk factor influencing clinical presentation, course and prognosis of ACS, in many studies[69,86].

About 20 percent of patients with MI have known diabetes. An even greater proportion of the MI patients have previously undiagnosed diabetes or impaired glucose tolerance when arriving in the CCU[70]. Diabetes is associated with markedly increased risk of MI and cardiovascular mortality in both women and men although women seem to be more vulnerable to the devastating effects of diabetes, which our data also indicate[53,62].

In our analysis the occurrence of atrial fibrillation (AF) influenced the long-term outcome negatively in both genders but only significantly in men. AF occurring after MI may occur alone or in association with other complications. The prognostic significance of new-onset AF in patients with ACS has been determined lately and AF is found to be an independent predictor of a worse outcome[87,88]. However, limited information is available about the different impact of AF in gender. Further efforts to identify these high-risk patients are needed so that appropriate therapies can be targeted to this high-risk cohort in order to improve their hospital and, potentially, long-term outcomes.

Treatment with diuretics was, much to our surprise, associated with a poorer long-term outcome for men but not for women. Diuretic treatment at entry was more common among women. It is well-known that diuretics are quite often prescribed to women as antihypertensive drugs whereas other treatment strategies are chosen in men[89]. Men treated with diuretics on admission to hospital, had probably correctly been diagnosed with heart failure, which may explain their poor outcome. A man on diuretics might be in a poorer condition compared with a woman, where diuretics often have been prescribed due to breathlessness and leg oedema without association with CHF, or for treatment of hypertension.

Coronary revascularization (PCI/CABG) during index hospitalization was associated with improved long-term survival in men in our study, an observation consistent with the GRACE risk model and the PRAIS UK Registry[90,91]. In contrast, previous CABG was significantly associated with death in men and a clear trend in the same direction was seen in women.

ST-depression on admission emerged as a risk factor for death long-term in both gender in our analyses. Data from the GUSTO IIb study, including the entire spectrum of ACS, indicate a higher early mortality in those presenting with ST-elevation compared with ST-depression. By 20 days the mortality curves had crossed and at 6 months mortality was higher in patients with ST-depression compared with ST-elevation[92].

Findings in Relation to Type of Syndrome

The majority of recent studies have focused either on MI patients or patients with non STEMI ACS and only a few have included patients with a broader range of ACS's[33,93]. Thus, studies on a population like ours including patients covering the entire spectrum of ACS are scarce. In our study patients with STEMI delayed seeking care less often than other patients with ACS and this condition was most frequently associated with impaired hemodynamics, findings that are in accordance with previous reports[94]. Patients presenting with less severe type of ACS in our study, were to a larger extent burdened with a previous cardiovascular history and heavy ongoing medical treatment, reflecting prior contact with medical facilities. In this respect there was a distinct difference between patients with STEMI and those with UAP, with the non STEMI patients in between. In agreement with these findings, most trials on ACS without ST elevation report a higher frequency of risk factors and previous diseases than trials on STEMI[95].

The proportion of patients being reperfused was somewhat higher in our study compared with others. Thrombolytic therapy was given in 38% of patients with STEMI and primary PCI was performed in 32%. In the large Euro Heart Survey of ACS, 35.1% received fibrinolytic therapy and 20.7% PCI and in GRACE study from 2002 the corresponding figures were 47% and 18 %, respectively[96,97].

There have been great advances in the management and care of patients suffering from all types of ACS during recent years. One could argue that our data are fairly old and therefore not relevant for ACS patients of today. However, the frequencies of

coronary angiographies as well as revascularization procedures were quite high in patients with non STEMI ACS in our study and well comparable with more recent figures from studies on ACS[77]. This means that the treatment strategies we applied in our patients are in congruence with how many ACS patients in Sweden and Europe are handled today.

The more frequent use of intravenous medical therapy in our study was due to a higher rate of complications in STEMI patients, compared with non STEMI patients. Other authors report the same finding[96]. When our study was conducted, the early intervention strategy, recommended by current guidelines, was not fully implemented and consequently the highest frequency of coronary angiography, PCI and CABG, was seen in women and men with UAP. However, in most respects, the non STEMI patients had more similarities with the STEMI patients than with the UAP patients.

The hospital death rate for patients in thrombolytic trials such as GRACE study and the Euro Heart Survey (EHS) is 7% which is considerably lower than the death rate for patients with STEMI in our study (11.6%)[77,96,97]. The fact that we included patients who were dying on admission may contribute to the high hospital death rate in our STEMI group. The mortality at 30 days was nearly twice as high in patients with STEMI compared with non STEMI patients. The hospital and 30 day mortality rates in the other types of ACS were lower than the rates found in GRACE study, probably due to our easy access to an on-site facility for cardiac catheterization and thoracic surgery.

Relatively limited data are available on the long-term outcome in patients with the whole spectrum of ACS and classified according to modern principles. The patients that did worse in the long run were those with non STEMI. In contrast, the outcome for STEMI patients, who did worse in the acute phase, was comparable to that among patients with UAP. This result is in line with older reports on unfavourable outcome in patients with non Q-wave MI and there are also a couple of recent reports on patients categorised according to modern principles, like our study, with similar findings[98,99]. As already described patients with non STEMI were treated less aggressively than patients suffering from UAP at the time of inclusion in our study. The UAP group was more often subjected to coronary angiography and revascularisation procedures. In a comparison between non STEMI and STEMI with adjustment for age and prognostic factors, one at a time, adjustment for two of the factors, ST-depression on ECG on admission and revascularization with PCI, resulted in a decreased difference in long-term mortality between non STEMI and STEMI. Thus, one reason for the high mortality in our non STEMI group might be the low rates of early intervention. The fact that patients with non STEMI have a poorer long-term outcome compared with other types of ACS, have also been previously explained by a greater burden of associated co-morbidities and differential pathogenesis[15]. Patients with non STEMI in our study were to a larger extent burdened with previous MI, heart failure, AF and diabetes. Variable risk burden, stresses the importance of aggressive risk analyses and treatment of ACS during the acute phase, with emphasis on patients with non STEMI as a group at high risk.

There are limited data on morbidity after hospitalization for ACS. Our figures indicate an overall relationship between type of syndrome and readmission due to MI, non elective revascularization and cardiovascular mortality. An age adjusted comparison within 45 months between non STEMI and STEMI, show significant differences for acutely performed revascularization.

Findings in Relation to Quality of Life

Quality of life (QoL) is an area of study that has attracted an ever increasing amount of interest over the past decades. A substantial number of studies have been performed in patients with MI[69,100]. Studies comparing QoL in patients with unstable angina and MI are few. In this study, covering the whole spectrum of ACS, we found a diagnosis of unstable angina associated with a poorer QoL than that of MI. Furthermore, our data indicate that it is the subgroup of patients with estimated low prognostic risk that experiences the poorest QoL. Our findings also indicate that factors in the patients' characteristics and history influenced the QoL after the acute event more than clinical course and treatment during the hospital phase.

Among patients and laymen MI has always been considered as a very serious and life threatening condition. To be labelled MI might therefore from a psychological point of view have negative consequences for the patient and his QoL. Our study was not designed in order to capture patients' reactions due to the diagnosis UAP or MI. We have no specific information about the perceived severity of disease among patients. Based on previous reports, a poorer QoL would have been expected in MI than UAP patients rather than the other way round. In order to avoid any potential influence from the diagnosis as such, the diagnosis at discharge was accepted without modification in our primary analysis. In some patients labelled as unstable angina the levels of CKMB or cardiac troponin T indicated that myocardial necrosis had occurred. Since our study was conducted before the latest guidelines for MI definition, a considerable number of those with unstable angina of high risk type should today have been diagnosed as MI. The fact that we did not find a poorer QoL in MI patients compared with UAP patients is reassuring. Due to the new definition of MI, an increasing number of ACS patients labelled with MI instead of UAP will be seen in the near future, which most probably won't have a negative effect on QoL.

In accordance with the FRISC II trial, patient characteristics and previous history appear to be of greater importance for well-being at 3 months compared with the in-hospital course[101]. On the whole, the burden of previous diseases was larger in our UAP patients compared with MI patients.

Depression is an important risk factor for declining health in patients with ACS. In many recent studies, depression emerges as an important risk factor in terms of both cardiovascular morbidity and mortality and health-related QoL[102]. A substantial number of patients meet with depression following an acute coronary event. Our study was not designed to provide a satisfactory measure of depression, although questions related to depression are represented in the second domain of our CHP questionnaire. It is very likely that depression contributed to a poor QoL in some patients.

The symptom angina as such was more frequent among the UAP patients than those with MI in our study and seemed to impair the QoL. These findings are in line with previous studies[69,100,103] . In several reports, improvements in QoL have been described after interventions in patients with both stable and unstable coronary disease and these improvements were found to be attributed to improvements in angina grade[32,104]. Besides the symptom angina as a predictor of poorer QoL, perceived cognitive function correlated to worse QoL in our study. Perceived cognitive function "reflecting a person's perception of his or hers ability to select relevant information, and to understand, retain, express and apply knowledge in specific contexts", has recently by Kiessling et al been evaluated as a predictor of worse QoL[23]. Perceived cognitive function was found to be the major determinant explaining a large proportion of the QoL, while only a small proportion was explained by perceived

physical functions/general health. Physical function but not cognitive function was related to CCS class. Perceived cognitive function was not related to the severity of the chest pain symptoms. Kiessling et al pointed out the importance of a QoL questionnaire including items reflecting cognitive function. The CHP instrument appears to be more sensitive, at least in some intervals, including questions about QoL in a broader perspective than most other instruments[105].

Our findings that patients with low-risk ACS reported the poorest QoL are extremely important. These patients did not experience fewer anginas, but, in the absence of objective signs of acute ischemia, a conservative approach was chosen in many of these cases. Although a considerable number of patients were subjected to coronary angiography and PCI, they were less often scheduled for speedy invasive treatment than high risk UAP patients. One might ask whether the lack of attention, both with respect to interventions and invitations to rehabilitation programmes, which were mainly given to infarct patients, contributed to the low QoL associated with UAP of low risk type. They received less attention from health care professionals and even less support from relatives and friends than their high risk counterparts. Patients with low-risk angina spent a very short time in hospital and at discharge they got less detailed information. When home they feel uncertain as to the origin of pain and they have got inadequate information about disease mechanisms. In the future, we should consider that the current guidelines for treatment of ACS stress the importance of risk stratification and early identification of high risk patients. With a strict focus on outcome with respect to hard end–points we run the risk of neglecting the low risk patients. Their needs may be different but they certainly also should be given full attention and a careful follow up.

Findings in Relations to Age

Elderly patients, those 65 years of age and older, represent a large proportion of western populations. They account for a considerable number of hospital admissions for ACS and deaths from MI. Despite the greater risk of MI among older patients and the increasing size of this population, the relationship between age, clinical presentation and outcome of MI in elderly patients is not completely understood.

The present study was not specially designed to study ACS in elderly people. Being part of a larger project with focus on long-term prognosis and risk in an ACS population treated in a CCU, the upper age limit for inclusion was set to 80 years.

In contrast to the findings in the GRACE registry that older patients delay seeking care more than younger patients, we observed no significant differences in this respect between the three age groups[46,94]. Our elderly also seemed to use the mobile coronary care unit to the same extent as the younger ones.

In accordance with previous reports, we found a history of heart failure, previous MI and hypertension to be more common with increasing age, while hyperlipidemia, current smoking and prior PCI were considerably lower in the older age group[26]. Higher age was associated with less frequent use of coronary angiography and reperfusion therapy. Among all patients treated with reperfusion therapy, thrombolysis was the first preferred choice in elderly. Thus, also in our CCU, in line with suggestions from previous reports, elderly patients were less likely to undergo revascularization and to receive acute and long-term evidence-based medications when hospitalized with ACS[26,49,106]. The question is why? Are the lower rates of aggressive treatment due to elderly patients' increased number of co-morbid conditions, physician or hospital effects, or true age-associated variation? The fact that evidence supporting the efficacy of acute reperfusion therapy in elderly with acute

MI is not as strong as it is in younger groups may play some role. More data are available for thrombolysis than for PCI[107]. This is not true for other medications and actually, apart from the prescription of statins, there was no obvious under use of discharge medication related to age in our study. Our older patients received beta-blockers and ACE inhibitors to a similar extent as the younger patients.

Instead of the under-utilisation of evidence-based therapies in the oldest group, these patients may due to their increased risk profile, benefit from application of medically proven therapy aiming at reducing the burden of disease to an even greater degree than in younger patients. In our study as in a number of previous reports, older patients had a more complicated clinical course and a higher mortality than younger ones[37,46,49]. Short-term mortality as well as late mortality increased with age. Although age is an independent predictor of morbidity and mortality following acute MI, suboptimal management may further contribute to the high mortality in these patients. Our findings emphasize the ongoing need to better define and promote optimal therapeutic regimens for elderly patients with ACS.

SUMMARY

- Women are struck by ACS at a higher age than men and were, in the CCU setting, as likely to present with ST-elevation MI (STEMI). They were less likely to present early for hospital care and were attended to less rapidly in the emergency department. Women had lower rates of prior MI and prior coronary artery bypass surgery (CABG) than men but similar rates of percutaneous coronary interventions (PCI). At younger ages women were more likely to present with hypotension.

- The management strategies including coronary angiographies and reperfusion therapy appeared to be similar in women and men, although a non-significant tendency of using PCI more often in men was observed. The only gender difference regarding treatment was CABG planned on discharge, which was more common in men. Women did not suffer from more severe complications or earlier death.

- Among women and men surviving the acute phase of an ACS there was no difference in long-term mortality, while rehospitalization due to heart failure was higher in women before, but not after adjustment for age.

- Out of a number of variables significantly associated with a poorer outcome, diuretic treatment prior to admission seemed to have a larger impact on prognosis in men and elevated creatinine to be of more importance in women.

- Patients presenting with less severe type of ACS, UAP rather than MI, were to a larger extent, burdened with a previous cardiovascular history and heavy ongoing medical treatment. However, smoking was most common in STEMI

- Severe complications including early mortality was associated with STEMI, while in the long run non STEMI patients had a poorer outcome than the other types of ACS.

- After adjustment for co-variates the survival disadvantage for non STEMI disappeared. In addition to age, ST-depression on admission and revascularization with PCI seemed to have been of particular importance, indicating that a low rate of early interventions in the non STEMI group could be a factor of importance for a poor outcome.

- Elderly patients were less frequently subjected to coronary angiographies and PCI. They had a more complicated clinical course and a poorer outcome.

- Patients with unstable angina pectoris, especially of the low-risk type, experienced poorer quality of life following ACS than patients with other types of ACS

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APPENDIX

Domains and items in the Cardiac Health Profile questionnaire (CHP)

Domains **Items**

- **----------**
- ***Perceived cognitive function***
- **1. How do you cope with tasks that require concentration and reflection?**
- **2. Are you an active person, full of initiative or passive and listless?**
- **3. Do you easily forget things in the immediate past or where, for example, you have placed things?**
- **4. Do you easily understand and solve problems, make decisions, adapt to new situations?**
- ***Emotional function***
- **5. Do you feel depressed or have difficulty finding pleasure in things you used to find pleasant?**
- **6. Do you easily become irritated, sad, worried, or anxious?**
- **7. Do you often experience fear, uneasiness or anxiety?**
- **8. Do you easily lose control over your feelings?**
- ***Social function***
- **9. Are you satisfied with your sleep (quality of sleep, ability to fall asleep etc.)?**
- **10. Do you have a good relationship with those connected to you (family and friends)?**
- **11. Are you satisfied with your daily life (at work, as a pensioner, as a housewife, as a student, etc.)?**
- **12. Do you experience your leisure time as meaningful and enriching?**
- ***Physical function/general health***
- **13. How is your sexual life?**
- **14. Are you satisfied with your physical capacity to accomplish things you wish to do?**
- **15. How do you experience your general health status?**
- **16. Are you troubled by various kinds of pain other than your known anginal chest pain?**
- **The answers are marked on a 100 mm VAS scale with verbal anchors. High scores indicate a**
- **poorer Quality of Life.**

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